REMARKS

The disclosure stands objected to because blanks are present in the specification on pages 4, 5, and 28 for ATCC and hybridoma designations of the CTLA4 antibodies. Applicants respectfully request that the objection be held in abeyance until such time as there is allowable subject matter.

Status of the Claims

Claims 2-11 and 13-24 are pending. Claims 16-23 have been withdrawn from further consideration by the Examiner as being drawn to a non-elected invention. Claims 2-11, 13-15 and 24 are currently under consideration. Claim 2 has been amended to more particularly point out the invention. Support for the amendment is found in the specification on page page 80, lines 3-19; Figure 4a and 4b.

Written Description Rejection Under 35 U.S.C. § 112

Claim 7 stands rejected under 35 U.S.C. § 112 first paragraph, as allegedly failing to comply with the written description requirement. The Office alleges that the specification provides no written support for the term "reduced binding of the antibody to the human CTLA4 with the substitution of amino acid 83." Applicants respectfully traverse this rejection. Support for the term is found in the specification on page 79, lines 2-5, which states: "Substitution of alanine (A) for glutamic acid (E) at position 46 (position 83 of SEQ ID NO: 2) drastically affects binding of antibody 26, 27, 34, 35, 36, and 38. In contrast the same substitution has little, if any, effect on antibodies 29, and 33." Support is also found in Figure 2 and the description of Figure 2 found on page 5,

lines 22-25 of the specification. Figure 2 compares the binding of 3 CTLA4 specific monoclonal antibodies to wild type CTLA4 and a panel of mutant CTLA4 molecules.

The Office is reminded that there is no *in haec verba* requirement so long as the claim is supported in the specification through express, implicit or inherent disclosure. M.P.E.P. §2163.

The Rejections Under 35 U.S.C. § 102(e)

Claims 2-7, 10-13 and 24 are rejected under 35 U.S.C. § 102(e) as allegedly anticipated by Korman et al. (US 2002/0086014 A1) ("Korman"). Claims 2, 10, 11, 13 and 24 are rejected under 35 U.S.C. § 102(e) as allegedly anticipated by Lowman et al. (U.S. Patent No. 5,994,511) ("Lowman").

A. The Anticipation Standard

The standard required for finding anticipation under 35 U.S.C. § 102(e) is stated in MPEP § 2131 (emphasis added). "'A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference.' *Verdegaal Bros. v. Union Oil Co. of California*, 2 U.S.P.Q.2d 1051, 1053 (Fed. Cir. 1987). 'The identical invention must be shown in as complete detail as is contained in the . . . claim.' *Richardson v. Suzuki Motor Co.*, 9 U.S.P.Q.2d 1913, 1920 (Fed. Cir. 1989)." Neither Korman or Lowman meet this standard.

The Korman Reference

The Office alleges that Korman teaches anti-CTLA-4 antibodies, including monoclonal and humanized antibodies, including conjugated therapeutic moieties, such as chemotherapeutics and toxins. The Office also alleges that Korman teaches soluble

IgG antibodies to CTLA-4. The Office admits, however, that naked soluble antibodies promote the expansion of T cells.

Claim 2 has been amended to recite a soluble monoclonal antibody that is specifically reactive with CTLA4, wherein the antibody does not cause proliferation of a T cell. Korman does not anticipate the claimed invention because its does not disclose each and every element as set forth in the amended claim, either expressly or inherently. The Office has admitted that the soluble antibodies disclosed in Korman promote the expansion of T cells. The amended claims recite soluble monoclonal antibodies that do not cause proliferation of a T cell. Applicants submit that the amended claim is not anticipated by Korman and thus respectfully request withdrawal of the rejection.

The Lowman Reference

The Office alleges that Lowman discloses antibodies against a variety of antigens including CTLA4. The Office further alleges that Lowman discloses the antibodies can be conjugated, monoclonal and humanized. The Office also alleges that the claimed functional limitations would be inherent properties of the antibodies disclosed in Lowman. Applicants respectfully traverse this rejection.

Applicants submit that Lowman does not disclose a soluble monoclonal antibody that is specifically reactive with CTLA4, wherein the antibody does not cause proliferation of a T cell. Because Lowman does not teach each and every element as set forth in the claim, it cannot anticipate the amended claim.

Applicants further submit that the reliance on Lowman as an allegedly anticipatory reference is misplaced because Lowman never actually made a CTLA-4 specific antibody, but only disclosed a laundry list of candidates that include, but are not limited to, growth factors, clotting factors, microbial proteins, rheumatoid factors, and neurotrophic factors. Lowman further discloses a laundry list of possible modifications to antibodies, including, but not limited to mutating the variable region to improve affinity, mutating cysteine to serine to improve oxidative stability, fusion to heterologous proteins, fusion to therapeutic proteins, and fusion to prodrug activating enzymes. Thus, the skilled artisan is left to choose which antibody to modify in which way. Applicants urge the Office to consider *In re Arkley*, 455 F. 2d 586 (C.C.P.A. 1972); and *Akzo N.V. v. International Trade Commission* 808 F. 2d 1471 (Fed. Cir. 1986) where the courts have stated that anticipation is inappropriate under these facts, and at best the reference may be considered as part of an obviousness rejection.

For each of the reasons put forth above, Applicants respectfully request withdrawal of the anticipation rejection in light of Lowman.

The Rejections Under 35 U.S.C. § 103(a)

Claims 2-11, 13 and 24 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Korman et al. and/or Lowman in view of Hamann et al. (U.S. Patent No. 5,773,001) (Hamann). Claims 2-11,13 and 24 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 5,821,332 (Godfrey) and U.S. Patent No. 6,207,156 (Kuchroo) in view of Hamann.

The Claimed Invention Is Not Prima Facie Obvious

MPEP § 2143 provides the standard required to establish a prima facie case of obviousness. "First there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine what the reference teaches. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references combined) must teach or suggest all the claim limitations."

The motivation to make the claimed invention and the reasonable expectation of success must both be found in the prior art, not the Applicant's disclosure. *In re Vaeck,* 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991). The references must be considered as a whole and must suggest the desirability, and thus the obviousness of making the combination. *Hodosh v. Block Drug Co., Inc.,* 229 U.S.P.Q. 182, 187 n.5 (Fed. Cir. 1986); MPEP § 2141. The Patent and Trademark Office (PTO) bears the burden of initially establishing a prima facie case of obviousness. MPEP § 2142. The PTO has not met its burden in the instant case.

Korman and/or Lowman in View of Hamann

The Office alleges that Korman teaches anti-CTLA4 antibodies including antibodies conjugated to toxic moieties. The Office further alleges the antibodies can be monoclonal and humanized. The Office also alleges that Korman teaches anti-CTLA4 antibodies that block or antagonize signals transduced by human CTLA4, including interactions between CTLA4 and B7. The Office admits, however, that naked soluble antibodies promote the expansion of T cells. The Office further alleges that

Lowman teaches antibodies against a variety of antigens, including CTLA4. The Office admits that Lowman does not teach CTLA4 interaction with B7. The Office also alleges that Hamann discloses conjugation of a specific toxin (calcicheamicin) to a non-CTLA4 specific antibody. Applicants respectfully traverse this rejection.

The Cited References Do Not Teach or Suggest All of The Claim Limitations

Claim 2, as amended herein, recites "A soluble monoclonal antibody-toxic moiety conjugate comprising (a) an antibody that is specifically reactive with CTLA4, wherein the antibody does not cause proliferation of a T cell and (b) a toxic moiety." As discussed above, Korman does not teach all of the claim limitations because Korman does not disclose a soluble, monoclonal, non-multimeric CTLA4 specific antibody that does not cause proliferation of a T cell. None of the other cited references cure this defect. Lowman merely discloses the possibility of making antibodies that recognize many different antigens. CTLA4 is but one of a laundry list of such antigens. Nothing in Lowman suggests the possibility or desirablity of modulating an immune response with CTLA4 specific antibodies. Hamann does not disclose any CTLA4 specific antibodies at all, but instead discloses ACT4 specific antibodies conjugated to specific toxins. Missing from all of these references is a soluble monoclonal antibody, as described in claim 2, that does not cause proliferation of a T cell. Because combining the cited references does not teach or suggest all of the claim limitations, the claims are not obvious in light of Korman and/or Lowman in view of Hamann.

No Reasonable Expectation of Success Exists In Combining the Cited References

There would be no reasonable expectation of success in combining Kuchroo with Godfrey, because Godfrey discloses a CTLA4 specific antibody that is immunostimulatory. But nothing in any reference cited by the Office suggests conjugating a toxin to an immunostimulatory antibody would be successful. As admitted by the Office, the conjugated antibody to ACT4 disclosed by Godfrey was not immunostimulatory. As further admitted by the Office, the CTLA4 antibody disclosed by Kuchroo was. The Office admits that conjugation of a toxin to an antibody is supposed to target that cell for elimination. But nothing of record indicates that conjugating a toxin to a CTLA4 specific antibody would be successful, given that Kuchroo discloses that CTLA4 specific antibodies cause T cells to proliferate (i.e. are immunostimulatory). The Office suggests combining two compositions which have opposing outcomes (i.e. a toxin which eliminates cells combined with an antibody that causes the same cells to proliferate). At best, the combination might be merely obvious to try, but there was certainly no reasonable expectation of success that the combination would be successful. Obvious to try, however, is not the standard under 35 U.S.C. § 103. *In re O'Farrell*, 7 U.S.P.Q. 1673, 1680 (Fed. Cir. 1988).

The Office states that "the ordinary artisan would have appreciated that even though in certain instances antibodies to CTLA4 may be used to enhance an immune response, CTLA4 could also serve as a target for the elimination of T cells when the T cells were participating in an undesired immune response" (Office Action dated January 26, 2004, page 9). But the Office points to no reference of record to support this

position. The Office is reminded that the reasonable expectation of success must be found in the cited references. *In re Vaeck,* 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991). Applicants submit the Office has not met its burden in this regard and respectfully request the rejection be withdrawn.

Applicants previously argued that no reasonable expectation of success existed in making the claimed combination because CTLA4 and ACT4 belonged to distinct families and each was a member of a distinct signaling pathway. In response, the Office argued the instant claims are drawn to a product and the motivation of the ordinary artisan to produce the instantly claimed product would not have been inhibited by the fact that CTLA4 and ACT4 belong to different families or by the uniqueness of ACT4. The Office further argued antibody linked toxins to a variety of receptor families were well known at the time of the invention and the identification of cell surface molecules expressed predominantly on activated T cells provided the artisan with the opportunity to selectively eliminate activated T cells. There is nothing of record to support any of these statements. The Office is respectfully reminded that the burden of establishing a prima facie case of obviousness rests with the Office. MPEP § 2142. Applicants request that the Office cite a reference to support its position. Alternatively, if the Office is relying on the personal knowledge of the Examiner to support its position, Applicants request the submission of an affidavit pursuant 37 C.F.R. §1.104(d). Without such support Applicants respectfully submit the rejection must be withdrawn.

No Motivation To Combine The Cited References Exists

A skilled artisan would not be motivated to combine the cited references because Godfrey and Kuchroo teach contradictory outcomes. Targeting a cell with a toxic moiety

attached to an ACT4 specific antibody is intended to eliminate the target cell. Targeting a cell with the CTLA4 antibody disclosed in Kuchroo is intended to make the target cell proliferate. The Office has not pointed to anything in either reference to establish why such a combination would be desirable. The references do not provide any motivation for a skilled artisan to combine them and the Office has not pointed to any knowledge generally available to a skilled artisan to suggest such a combination would be desirable. Accordingly, Applicants respectfully request withdrawal of the rejection.

Hamann Combined With Godfrey And Kuchroo Does Not Render Claims 8 And 9 Prima Facie Obvious

Additionally, claims 8-9 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Godfrey, combined with Kuchroo in view of U.S. Patent No. 5,773,001 (Hamann). Claim 8 recites the toxic moiety is a carbohydrate. Claim 9 recites that the carbohydrate is calicheamicin. Hamann teaches antibodies conjugated with calicheamicin. Hamman does not teach targeting molecules expressed on activated T cells. Thus, Hamman does not teach targeting CTLA4. The Office relies on Hamann as allegedly teaching antibodies conjugated to carbohydrates generally, and calicheamicin specifically. Hamann, however, does not compensate for the deficiencies in the Godfrey and Kuchroo. A skilled artisan reading Hamann, would still have no reasonable expectation of success in combining Godfrey with Kuchroo, as Hamann only provides information on conjugating antibodies with calicheamicin—it does not address targeting CTLA4 or explain why an immunostimulatory antibody could be successfully conjugated to a toxin intended to kill the target cell of the antibody. Thus, claims 8 and 9 are not prima facie obvious.

Accordingly, for the reasons stated above Applicants respectfully request withdrawal of the rejection under 35 U.S.C. § 103(a).

CONCLUSION

In view of the foregoing amendments and remarks, Applicants respectfully request the reconsideration and reexamination of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to Deposit Account No. 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

Dated: February 2, 2005

By: Rebecca M. McNeill
Rebecca M. McNeill
Reg. No. 43,796